IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION		DOCKET NO.:	47679
OF:	VON DEYN ET AL.	CONFIRM. NO.:	4798
SERIAL NO.:	09/091,300	GROUP ART UNIT:	1626
FILED:	JUNE 16, 1998	EXAMINER:	R. H. HAVLIN

FOR: 3-HETEROCYCLYL-SUBSTITUTED BENZOYL DERIVATIVES

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

1. I, Matthias Christian Witschel, a doctor of natural sciences, a citizen of the Federal Republic of Germany and residing at Höhenweg 12B, 67098 Bad Dürkheim, Germany, declare as follows:

1.a) I am a fully trained chemist, having studied chemistry at the University of Erlangen-Nuremberg, Germany, from 1985 to 1994;

1.b) I was awarded my doctor's degree by the University of Erlangen-Nuremberg in 1994; I was a post-doctoral fellow at the Stanford University from 1994 to 1995;

1.c) I joined BASF SE, formerly named BASF Aktiengesellschaft of 67056 Ludwigshafen, Germany, in 1996, and since then I have been engaged in the synthesis of herbicides and herbicide screening, and I am therefore fully conversant with the technical field to which the invention disclosed and claimed in application Serial No. 09/091,300 belongs;

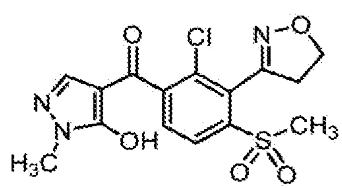
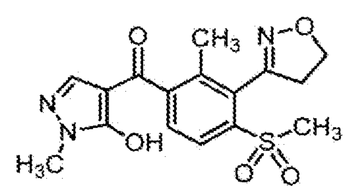
1.d) I am the Matthias Witschel who is named as one of the inventors of the invention disclosed and claimed in Application No. 09/091,300, and the Matthias Christian Witschel who executed the Declarations previously filed in this application on October 21, 1999, and signed by me on October 21, 1999 ("Declaration 1", 4 pages, and "Declaration 2", 11

pages), and the Declaration filed in this application on January 03, 2012, and signed by me on December 14, 2011 ("Declaration 3"); therefore, I am familiar with the prosecution history of the application and with the prior art cited therein.

2. I have studied the Office actions which issued in this case on November 24, 2010, on August 01, 2011, and on August 20, 2012 ("First Office action," "Second Office action," and "Third Office action," respectively), and the references cited therein, in particular the teaching of ***von Deyn et al.*** as provided in ***WO 96/26206*** and the U.S. counterpart thereof, ***US 5,846,907*** ("***von Deyn***"), as well as the disclosure of ***Silverman*** regarding "*Drug Discovery, Design, and Development*" in Chapter 2 of "The Organic Chemistry of Drug Design and Drug Action," Academic Press, Inc. San Diego 1992, pp. 4-51 ("***Silverman***"). I have also studied Chapters 1 (Preliminary Description of Error Analysis) and 2 (How to Report and Use Uncertainties) of ***Taylor***, "*An Introduction to Error Analysis*," University Science Books, Sausalito 1997, 2nd Ed., pp. 1-43 ("***Taylor***") enclosed with the Third Office action.

2.a) It is my understanding that the Office actions question whether the difference in efficacy between the prior art compounds and those delineated, e.g., in Claim 28 of the application is of both practical and statistical significance.

2.b) To further show the practical and statistical significance of the difference in efficacy I compiled all data available from side-by-side standard testing of the following compounds **5.5*** (comparative) and **3.86** against three key corn-weeds *Brachiaria plantaginea* ("BRAPL"), *Amaranthus retroflexus* ("AMARE"), and *Abutilon theophrasti* ("ABUTH") as well as the crop plant corn ("ZEAMX) in post-emergence treatment.

 **5.5*** (comparative)	 **3.86**
Compound 5.5 US 5,846,907 (***von Deyn***), col. 29, Table 5	Compound 3.86 Ser. No. 09/091,300, Table 3, p. 133

3. The side-by-side post-emergence standard testing was conducted under the following conditions:

3.a) Plastic flowerpots containing loamy sand with approximately 3.0% of humus as substrate were used as culture containers. The seeds of each test plant species were sown in separate culture containers.

3.b) The test plants were sown and grown in the containers a few days prior to treatment. After reaching a height of 3 to 15 cm, depending on the plant habit, they test plants were treated with the compounds which had been suspended in water, using standard formulation additives.

3.c) The plants were kept at 20 – 35 °C in the greenhouse. The test period extended over 21 days. During this time, the plants were tended, and their response to the individual treatments was evaluated.

3.d) Evaluation was carried out by rating the damage to the plants on a scale from 0 to 100. A rating of 100 means complete or 100% destruction of at least the aerial parts of the plant, and a rating of 0 means no damage, or normal course of growth, as compared to a non-treated control sample.

3.e) In all cases the compounds **5.5*** and **3.86** were tested side-by-side in identical assays and under identical application conditions. Repeat side-by-side tests were conducted on different application dates but using the same assays and conditions.

3.f) The collected data are compiled in the following table:

Compound **5.5***					Compound **3.86**				
Dose	BRAPL	AMARE	ABUTH	ZEAMX	Dose	BRAPL	AMARE	ABUTH	ZEAMX
		40					60		
			50	15				70	20
		60	65	0			80	80	10
			75	0				85	0
15.63		60			15.63		80		
	80	70	85	10		90	90	95	0
	80	80	70	0		85	98	90	0
	70	90	80	10		95	95	90	0
	70	70	80	20		98	90	100	0
	98					100			
	98					98			
	98					98			
		50					65		
			80	20				80	20
		70	80	10			85	80	10
31.25			80	10	31.25			85	0
		65					85		
	85	75	95	10		90	90	98	20
	80	90	80	0		90	98	95	0
	70	98	90	10		95	98	95	0
	90	95	85	20		100	100	100	0
	85	100	55	20		95	100	85	10
	95	98	60	10		90	98	80	0
	98					100			
	100					98			
	98					98			
		65					65		
			85	30				80	30
		80	85	20			85	85	25
62.5			80	15	62.5			85	10
		80					85		
	85	80	95	25		90	95	98	30
	95	90	85	10		98	98	95	0
	98	98	90	15		98	98	98	0
	100	100	80	20		100	100	100	0
	85	100	75	20		95	100	85	30
	95	98	70	20		90	98	85	20

Compound **5.5***					Compound **3.86**				
Dose	BRAPL	AMARE	ABUTH	ZEAMX	Dose	BRAPL	AMARE	ABUTH	ZEAMX
125	98				125	100			
	100					100			
	98					98			
		65					65		
			85	50				80	50
		85	85	30			90	85	40
			80	50				85	20
		80					85		
	100	98	90	15		100	98	95	0
	95	98	80	30		90	98	90	20

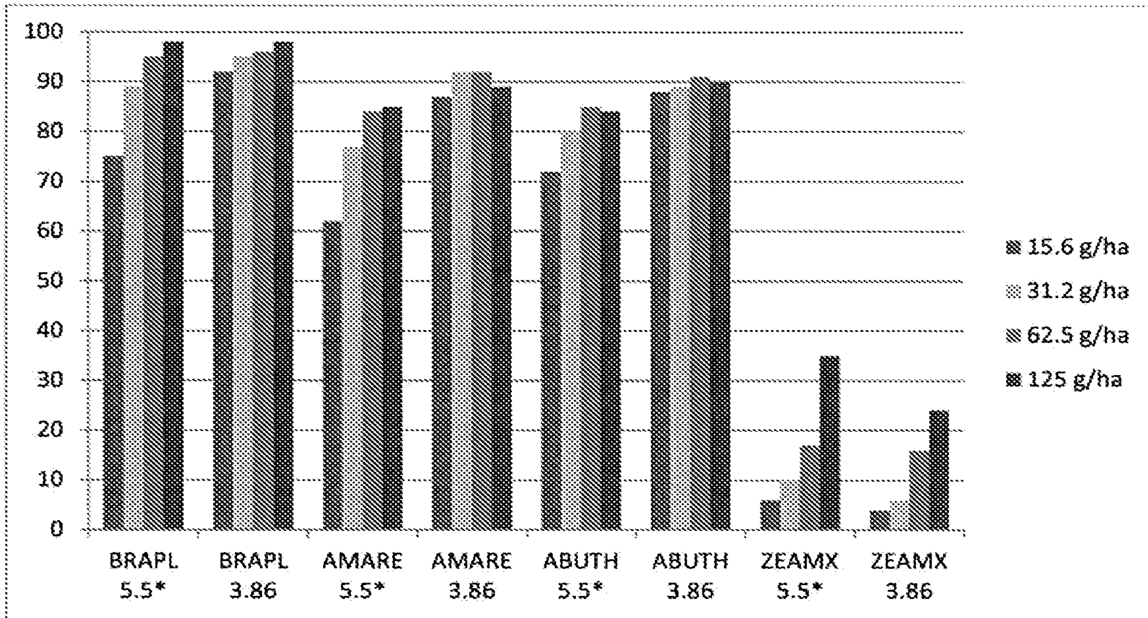
4. To evaluate the statistical relevance of the test results, the ratings determined in the individual side-by-side tests were averaged. The averaged results are compiled in the following Table 1:

Table 1: Averaged Efficacy Ratings of Compounds **5.5*** (comparative) and **3.86**

	BRAPL		AMARE		ABUTH		ZEAMX	
Compound	**5.5***	**3.86**	**5.5***	**3.86**	**5.5***	**3.86**	**5.5***	**3.86**
15.6 g/ha	75 (4)	92 (4)	62 (7)	87 (7)	72 (7)	88 (7)	6 (7)	4 (7)
31.2 g/ha	89 (9)	95 (9)	77 (9)	92 (9)	80 (9)	89 (9)	10 (9)	6 (9)
62.5 g/ha	95 (9)	96 (9)	84 (9)	92 (9)	85 (9)	91 (9)	17 (9)	16 (9)
125 g/ha	98 (5)	98 (5)	85 (5)	89 (5)	84 (5)	90 (5)	35 (5)	24 (5)

In Table 1, the number preceding the parenthesis signifies the averaged efficacy rating, and the number in parenthesis is the number of side-by-side tests at the respective application rate that were averaged. E.g., the indication "75 (4)" in col. 2, row 3, of Table 1 means that the results of four (4) tests in which compound **5.5*** was applied post-emergence at an application rate of 15.6 g/ha to *Brachiaria plantaginea* ("BRAPL") were averaged, and the damage to the plants was on average 75%.

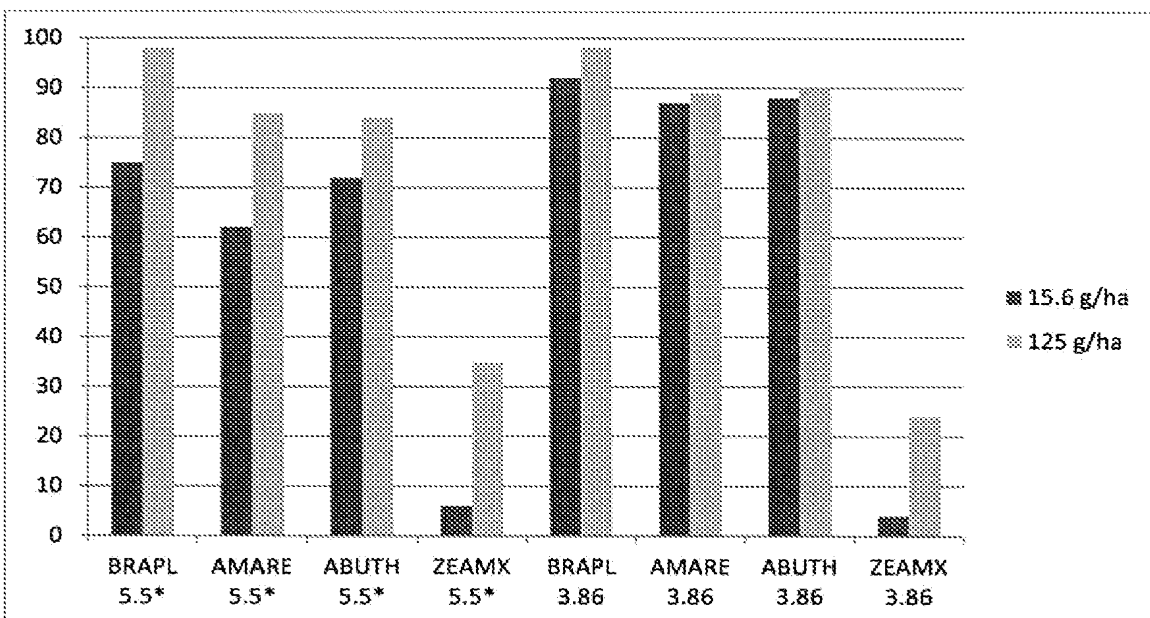
4.a) To better be able to visualize the data, the foregoing averaged efficacy ratings were charted as follows:



4.b) The averaged efficacy ratings compiled in Table 1 and depicted in the chart show that, at an application rate of 15.6 g/ha, compound **3.86** is on average more effective against AMARE and ABUTH than compound **5.5*** at eight times the application rate, i.e., 125 g/ha. The averaged ratings also show that, in the investigated interval of application rates, the loss in efficacy against the weeds which results when lowering the application rate is more pronounced for the comparative compound **5.5*** than compound **3.86**. For example, the difference between the averaged efficacies of comparative compound **5.5*** against AMARE at application rates of 15.6 and 125 g/ha is (85 - 62 =) 23 whereas the corresponding difference is (89 - 87 =) 2 control for compound **3.86**, and the difference between the averaged efficacies of comparative compound **5.5*** against BRAPL at application rates of 15.6 and 125 g/ha is (98 - 75 =) 23 whereas the corresponding difference is (98 - 92 =) 6 for compound **3.86**. Contrastingly, the damage to the corn plant "ZEAMX" diminishes drastically for both compounds when the application rate is reduced. That is, the difference between the averaged damage to corn caused by comparative compound **5.5*** at application rates of 15.6 and 125 g/ha is (35 - 6 =) 29 whereas the corresponding difference is (24 - 4 =) 20 for compound **3.86**.

4.c) Additionally, the averaged efficacy ratings show that, at any one of the given application rates, compound **3.86** is more effective against the weeds and/or is less damaging to corn, than comparative compounds **5.5***. This means that compound **3.86** is on average more selective in corn than comparative compound **5.5*** at all of the investigated application rates. On the one hand, the respective trend is apparent when the differences between the averaged efficacies of comparative compound **5.5*** against the weeds BRAPL, AMARE, and ABUTH, and the crop ZEAMX at application rates of 15.6 and 125 g/ha (23, 23, 12, and 29, respectively) is compared to the corresponding differences found for compound **3.86** (6, 2, 2, and 20, respectively). Accordingly, reducing the application rate of the comparative compound **5.5*** from 125 to 15.6 g/ha significantly reduces the damage to the crop plant but at the same time reduces the herbicidal effect against BRAPL and AMARE almost to the same extent. When the application rate of compound **3.86** is reduced from 125 to 15.6 g/ha, the damage to the crop plant, also, is significantly reduced. However, the herbicidal effect against BRAPL, AMARE, and ABUTH is only slightly affected by the lowered application rate.

The respective trend is further illustrated by the following chart of the averaged efficacy ratings at application rates of 15.6 and 125 g/ha:



The chart also illustrates that the improved selectivity, i.e., the difference between the herbicidal effect on weeds and the damage to the crop, of the compound **3.86** becomes more pronounced as the application rate is decreased.

5) To evaluate the statistical significance of the efficacy ratings a two-parameter logistic model was employed:

$$Injury\,(dose, ED50, stp) = 100 - \frac{100}{\left[1 + \left(\frac{dose}{ED50}\right) ** \, stp\right]} \qquad \text{Eq 1}$$

The model yields no damage at low doses and 100% damage at high doses.

ED50: effective dose at 50% injury

stp: steepness (parameter, which is quantified by the slope of a dose-response curve). See, for example, Christian Ritz, Environmental Toxicology and Chemistry, Vol. 29, No. 1 (2010) pp.220-229, Eq. 2 (copy attached).

All original (measured) data were amended by including an artificial, reasonable data point of 0% injury at 1×10^{-5} g/ha and fitted using Eq.1. For the null hypothesis that assumes that both compounds are equally active all data from both compounds were combined in one model for each plant. For the alternative that both compounds are not equally active, a separate model was fitted for each combination of the individual compound and plant. The resulting efficacy ratings at the given application rates are summarized in Table 1a:

Table 1a: Predicted Efficacy Ratings of Compounds **5.5*** (comparative), **3.86** and of null hypothesis (marked as $^{\#}$)

	BRAPL		AMARE		ABUTH		ZEAMX	
Compound/ application rate	**5.5***	**3.86**	**5.5***	**3.86**	**5.5***	**3.86**	**5.5***	**3.86**
15.6 g/ha	75	92,1	69,6	85,3	72,9	82,9	6,62	4,01
	84,1#		77,5#		79,9#		5,26#	
31.2 g/ha	88,3	94,9	79,4	88,3	78,1	86	12	7,89
	91,4#		83,6#		83,3#		9,92#	
62.5 g/ha	95	96,7	86,6	90,7	82,5	88,6	20,9	14,9
	95,5#		88,4#		86,2#		17,9#	

	BRAPL		AMARE		ABUTH		ZEAMX	
Compound/ application rate	**5.5***	**3.86**	**5.5***	**3.86**	**5.5***	**3.86**	**5.5***	**3.86**
125 g/ha	98	97,9	91,6	92,7	86,2	90,8	33,7	26,5
	97,7#		91,9#		88,7#		30,2#	

In each case, the fit quality was determined by the sum of squared differences between a measured injury and the injury predicted by the corresponding fit curve (Residual sum of squares, abbrev. RSS).

$$RSS = \sum_{i=1}^{n} (y_i - f(x_i))^2 , \qquad Eq. 2$$

wherein y_i is the injury measured in i^{th} experiment, $f(x_i)$ is the injury predicted in i^{th} experiment (see Table 1a), i is the number of experiment.

To evaluate the probability that compound **5.5*** is as active as compound **3.86** we used an F-test with 2 parameters for the Null hypothesis and with 4 parameters for the alternative according to which both compounds are not equally active:

F = (RSSeq-RSSsum)/(4-2)/(RSSsum/(Ndata-4))

Prob(≥F) = 1-pF(F,2,Ndata-4),

where pF(x,m,n) is the distribution function of the F-distribution with m and n degrees of freedom. The results are included in the following Table 1b:

Table 1b: Statistical Analysis

	BRAPL		AMARE		ABUTH		ZEAMX	
Compound/ application rate	**5.5***	**3.86**	**5.5***	**3.86**	**5.5***	**3.86**	**5.5***	**3.86**
RSS	1149	439	6429	4093	2749	1905	1958	4008
RSSsum	1588		10522		4654		5966	
RSS comp1 = comp2	2362		11994		6089		6351	
Ndata	54		60		60		60	
F value	12.1		3.9		8.6		1.8	
Pr(≥F)	4.9×10^{-5}		2.6×10^{-2}		5×10^{-4}		0.17	

In Table 1b, "RSS" is the residual sum of squares for each of the compounds separately; its sum is denoted by RSSsum; "RSS comp1 = comp2" is the RSS determined under the assumption that compound **5.5*** and **3.86** have the same activity; Ndata is the number of measurements and Pr(≥ F) is the probability that compound **5.5*** is as active as compound **3.86**.

5.a) According to the residual sum of square analysis of the activity of compounds **5.5*** and **3.86** regarding, e.g., the weeds BRAPL and ABUTH, the probability that the comparative compound **5.5*** is as active as compound **3.86** is <0.1%, whereas this probability is below 3% in the case of the weed AMARE. This means that at these three plants it is statistically highly probable that compound **3.86** is significantly more active than the comparative compound **5.5***, as already suggested by the differences in averaged activity.

6. ***Silverman*** explains, on page 21, ll. 17-31, because a drug must get to the site of action, then interact with it, modifications made to a molecule may have one or more of the following effects:

i. Structural. If the moiety that is replaced by a bioisostere has a structural role in holding other functionalities in a particular geometry, then size, shape and hydrogen bonding will be important.

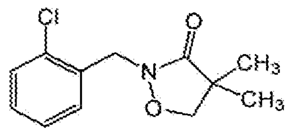
ii. Receptor interactions. If the moiety replaced is involved in a specific interaction with a receptor or enzyme, then all of the parameters except lipid and water solubility will be important.

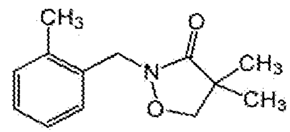
iii. Pharmacokinetics. If the moiety replaced is necessary for absorption, transport, and excretion (collectively, with metabolism, termed pharmacokinetics) of the compound, then lipophilicity, hydrophilicity, pK_a, and hydrogen bonding will be important.

iv. Metabolism. If the moiety replaced is involved in blocking or aiding metabolism, then the chemical reactivity will be important.

6.a) Further, as I explained and illustrated in my Declaration 3, the exchange of chlorine by methyl in a herbicidal compound is generally deemed to diminish the herbicidal effect.

Declaration 3, para. bridging pp. 5-6. Accordingly, US 4,405,357 illustrated the herbicidal effect of Examples 16 and 19:


Example 16


Example 19

The data which are compiled in Table 1 of US 4,405,357, at cols. 31-32, and cols. 33-34, show that the replacement of the ortho chlorine group of Example 16 by an ortho methyl group, as in Example 19, resulted in an almost complete loss of the herbicidal activity. Examples 16 and 19 of US 4,405,357 are illustrative of the teaching of ***Silverman*** that a structural modification of a lead compound along the lines of bioisosterism may affect the toxicity or the biological effect of a compound. In particular, Examples 16 and 19 of US 4,405,357 illustrate the negative impact on the herbicidal activity when a chlorine substituent is replaced by a methyl group.

6.b) In light of ***Silverman***'s explanations, and without wishing to be bound by theory, the impact of a replacement of chlorine by methyl on the herbicidal effectivity of a compound may be explained by the fact chlorine and methyl substituents differ significantly with regard to inductive effects on the aromatic ring to which they are bonded, as well as the molecular volume and the polarity, represented by the opposing Hammet coefficients (σ) for chlorine and methyl in para (σ_p) or meta (σ_m) position and field effect values (F):

Chlorine:	$\sigma_p = +0.24$	$\sigma_m = +0.37$	F = +0.72
Methyl:	$\sigma_p = -0.14$	$\sigma_m = -0.06$	F = -0.01

See "Advanced Organic Chemistry," Jerry March, 4th Ed., pp. 280 et seq., copy enclosed.

6.c) Alternatively or additionally, the difference the impact of a replacement of chlorine by methyl on the herbicidal effectivity of a compound may be explained by the fact that methyl-substituted compounds are prone to be metabolized differently than the corresponding chlorine-substituted compounds because methyl groups frequently are rapidly oxidized by Cytochrome P450 enzymes in plants. Such rapid metabolization could

be responsible for the lower herbicidal efficacy of methyl-substituted herbicides as compared to the corresponding chlorine-substituted counterpart.

6.d) Moreover, the physicochemical properties of the compounds may be affected significantly when replacing a chlorine substituent by a methyl group. For example, the logP or partition coefficient of compound **3.86** is 1.5 whereas that of compound **5.5*** is 0.1 and the pK_a for compound **3.86** is 3.7 and for compound **5.5*** is 3.0. The logP can be used as a measure of the lipophilic character of the compound. As noted by ***Silverman***, properties such as lipophilicity and pK_a play a role in the pharmacokinetics of the compound.

7) In light of the factors addressed in paragraphs 6.-6.d), it is surprising that compound **3.86** (which carries a *methyl* substituent) is more effective against the weeds than comparative compound **5.5*** (which carries a *chlorine* substituent in the corresponding position). It is also surprising that the effect the increased effectivity of compound **3.86** against the weeds is not equally reflected in the effect on the crop plant ZEAMX. Contrary to the trend in the data concerning the efficacy against BRAPL, AMARE and ABUTH, which show that the methyl substituted compound **3.86** is more effective than the chlorine substituted comparative compound **5.5***, the damage to the crop plant ZEAMX which is caused by the methyl substituted compound **3.86** is less severe than that caused by the chlorine substituted comparative compound **5.5***.

I, Matthias C. Witschel, further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued therefrom.

Date: 21.2.2013 Matthias C. Witschel

(Matthias C. Witschel)

Encls.